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PREVALENCE OF GENETIC SUSCEPTIBILITY FOR CELIAC DISEASE IN BLOOD DONORS IN SÃO PAULO, BRAZIL

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ABSTRACT - ***Background*** - Celiac disease is a permanent intolerance induced by gluten, which is expressed by T-cell mediated enteropathy, and has a high prevalence in the general population. There is evidence of a strong genetic predisposition to celiac disease. ***Objective*** - To determine the prevalence of genetic markers HLA-DQ2 and HLA-DQ8 in blood donors from São Paulo and measure human recombinant tissue transglutaminase antibody IgA class in HLA-DQ2 and HLA-DQ8 positive donors. ***Methods*** - A total of 404 blood donors from São Paulo city and Jundiaí were included in the study and signed the informed consent form. Information regarding diarrhea, constipation and abdominal pain in the last 3 months was collected. Determination of HLADQ2 and HLADQ8 alleles was performed in all participants and human recombinant tissue transglutaminase antibody class IgA was measured only in blood donors who presentedDQ2 and/or DQ8. ***Results*** - HLADQ2 and/or HLADQ8 were positive in 49% (198/404) of subjects. Positive samples were associated with alleles DR3, DR4, DR7, DR11 and DR12. The most frequent genotype was DR4-DQ8, which was present in 13.6% of samples, followed by genotypes DR3-DQ2 and DR7-DQ2 with DQB1*02 in heterozygous, which were present in 10.4% and 8.7%, respectively. Eleven out of 198 positive donors (5%) were positive to human tissue transglutaminase test. ***Conclusion*** - We observed a high prevalence of genetic markers for celiac disease, HLA-DQ2 and HLA-DQ8, in blood donors from São Paulo, similar to prevalence described in Europe. These findings show that the prevalence of celiac disease should not be rare in our country, but underdiagnosed.

HEADINGS - Celiac disease, genetics. Genetic markers. HLA-DQ antigens. Prevalence. Blood donors.

INTRODUCTION

Celiac disease (CD) is an autoimmune mediated enteropathy caused by a permanent intolerance to gluten in genetically predisposed individuals[12]. CD stands out among autoimmune diseases for having some of its etiopathogenic and physiopathologic factors known. This disease is triggered by an environmental factor, gluten. It is important to note that there are some disorders related to gluten that are not CD and present similar gastrointestinal symptoms[34]. In relation to the genetic factor, several *loci* have been correlated to CD, the most important *loci* described is CELIAC 1, located in the short arm of chromosome 6. In this region, there are the human histocompatibility antigen genes (HLA). Locus CELIAC 1 refers to alleles DQA1 and DQB1[6,20,35], which together codify a heterodimer antigen presented by the T CD4 lymphocytes. The importance of CELIAC 1 results from the fact that 90 to 95% of CD patients present DQ2 heterodimer and 5% to 10% of patients present DQ8 heterodimer[13,35,36].

Genetic predisposition to CD is clearly demonstrated in concordance studies on monozygotic (75%) and dizygotic (10%) twin couples, as well as by the high degree of family grouping of the disease[9].

DQ2 heterodimers are codified in cis by alleles DQA1*0501 and DQB1*0201. When it occurs, generally due to bonding unbalance, these alleles are transmitted together to allele DRB1*03, in the DR region. This haplotype is called DR3-DQ2. However, trans-positioned alleles, i.e., positioned in homologous chromosome, may also codify DQ2 heterodimer. This is the case of haplotypes DRB1*07-DQA1*0201-DQB1*0202 (DR7-DQ2) and DRB1*11-DQA1*0505-DQB1*03 (DR11-DQ2)[21,25,35].

DQ8 heterodimers are codified by alleles DQA1*0301 and DQB1*0302 and due to bonding unbalance, are transmitted together with allele DRB1*04, forming the haplotype known as DR4-DQ8[17,36,38].

Considering that almost all patients with CD present DQ2 and DQ8 heterodimers, these genetic markers together have a high negative predictive value[13].

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There are some studies, which evaluate the genetic predisposition in the general population, as the one carried out by Mäki et al., in Finland, that found the prevalence of 38.9% of the alleles associated to CD in 3627 students[18]. Alarida et al., carried out a study in North Africa with 156 healthy children, where 3.2% of DQ2 and DQ8, 7.7% DQ2 with DQB1*02 homozygous, 23% DQ2 with DQB1*02/X and 19% DQ8, 4.5% DQ8 with DQB1*02 homozygous were observed, and 14.7% did not present the DQ2 and DQ8 alleles[1].In Brazil, Silva et al.[33], found a frequency of 84% of DQB1*02 allele in 25 Brazilian patients with CD, while in the health individuals this allele was found in a frequency of 33%. Additionally, this study concluded that the alleles DQB1*02, DRB1*03 e DRB1*07 lead to a susceptibility to CD development in Brazilian patients. However, this study did not evaluate the prevalence of HLA-DQ2 and DQ8 in the studied population.

Considering advances in immunogenetics, the use of HLA-DQ2 and DQ8 typing as part of the diagnostic investigation for CD and the lack of studies regarding the genotype prevalence for HLA-DQ2 and DQ8 in a representative population in São Paulo, the objective of this study is to determine the prevalence of genetic markers HLA-DQ2 and HLA-DQ8 in blood donors from São Paulo and to perform serological assay for using human recombinant tissue transglutaminase antibody IgA class (anti-tTG) in HLA-DQ2 and HLA-DQ8 positive blood donors.

METHODS

The studied population included 9507 blood donors who donate between two different periods: from July 30th, 2010 to September 13th, 2010 and from March 24th, 2011 to October 18th, 2011.Considering the positivity frequency expectation of 40% for HLA-DQ2 and 8% forHLA-DQ8, assuming $P<0.05$ and 5% relative precision, the calculated sample size was 362 individuals. Since casuistic was not randomized, we selected 404 donors (10% over).

A transversal prospective study was carried out enrolling 404 volunteer blood donors, residents in São Paulo State. Samples were obtained following the inclusion criteria stipulated by the blood banks: healthy blood donors, who present good health, age between 18 and 65 years and weight over 50 kg. Candidates to blood donation excluded due to low hematocrit (under 36% for female and under 38% for male) were also included in this study, since their exclusion could artificially reduce the prevalence, once anemia is one of the clinical manifestations of CD. We selected the same number of male and female donors.

All candidates included in the study answered a form regarding the presence or absence of diarrhea, constipation, abdominal pain and weight loss in the last 3 months. Based on the weight and height, we calculated the body mass index (BMI) to correlate the underweight to CD predisposition.

Oral and written consent for participation in the project was requested. The study was conducted in accordance with our institutional ethical review.

Sample collection

For molecular tests,5 mL venous blood were collected in a Vacutainer® tube with EDTA, and for serological tracking, 9 mL in a Vacutainer® tube without anticoagulant. For molecular biology tests, samples were stored at 4°C and used within 72 hours. The serological samples were stored in a freezer at - 80°C for further performance of the human recombinant tissue transglutaminase IgA antibody and serum IgA determination, according to the positivity of the genetic tracking.

Molecular analysis

DNAextraction and genotyping were performed using DQ-CD Screen kit (BioDiaGene Molecular Biology Manufactory, Palermo - Italy) to screen the presence of DQ2 and/or DQ8 haplotypes. Positive samples were evaluated in the DQ-CD Typing Plus kit (BioDiaGene Molecular Biology Manufactory, Palermo - Italy) to classify the HLA class II.

Determination of HLA DQ2 and DQ8

The DQ-CD Screen kit (BioDiaGene Molecular Biology Manufactory, Palermo - Italy) detects samples DQ2 and/or DQ8 positive through a PCR Multiplex, which amplifies DQ2 and DQ8 alleles and an internal control.

For DNA extraction, 10 µL of total blood were mixed with 20 µl of Lysis Buffer and incubated for 5 minutes at room temperature. After, 180 µL of neutralization solution was added. Amplification process was performed adding 15 µL of a mix composed by 2 µL of extracted DNA and 18 µL of Taq Mix (provided by the kit), in a single microtube containing lyophilized primers specific to DQ2 and DQ8 alleles. PCR cycling was carried out in a thermal cycler according to the manufacturer's guidelines, and the amplification products were analyzed in agarose gel (Figure 1).

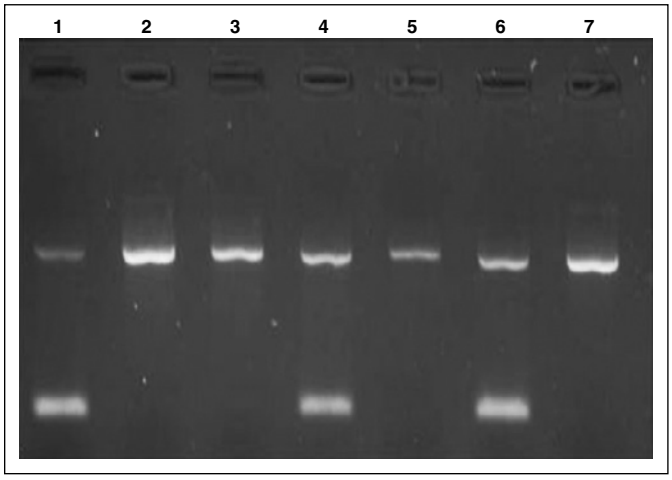

FIGURE 1. Eletrophoresis gel showing the internal control band (796bp) and DQ2 and/or DQ8 band (210pb). Lanes 1, 4 and 6 refer to samples DQ2 and/or DQ8 positive. Samples DQ2 and DQ8 negative are showed in lanes 2, 3, 5 and 7.

Classification of HLA alleles

After the evaluation of the results obtained from the DQ-CD Screen kit, all positive samples were submitted to the DQ-CD Typing Plus Kit (BioDiaGene Molecular Biology Manufactory, Palermo - Italy), which detects the HLA class II alleles related to the DQ2 and/or DQ8 molecules and CD: DQA1*0201, DQA1*03, DQA1*05, DQB1*02, DQB1*0301/04, DQB1*0302, DRB1*03, DRB1*04, DRB1*07, DRB1*11, DRB1*12. The test also detects the homozygous state of the DQB1*02 allele and have an internal control to validate the reaction.

For DNA extraction, 10μL of total blood with 20 μL Buffer Lysis were incubated at room temperature for 5 minutes and to interrupt the reaction 180μL of neutralization solution were added. A mix of 20 μL of the extracted DNA and 180μL of the Taq Mix solution was added in 12 PCR tubes containing lyophilized primers specific for each HLA allele studied. DNA amplification was carried out in a thermal cycler according to the manufacturer's guidelines and electrophoresis was performed in agarose gel (Figure 2). The results were analyzed according to the diagram provided by the manufacturer.

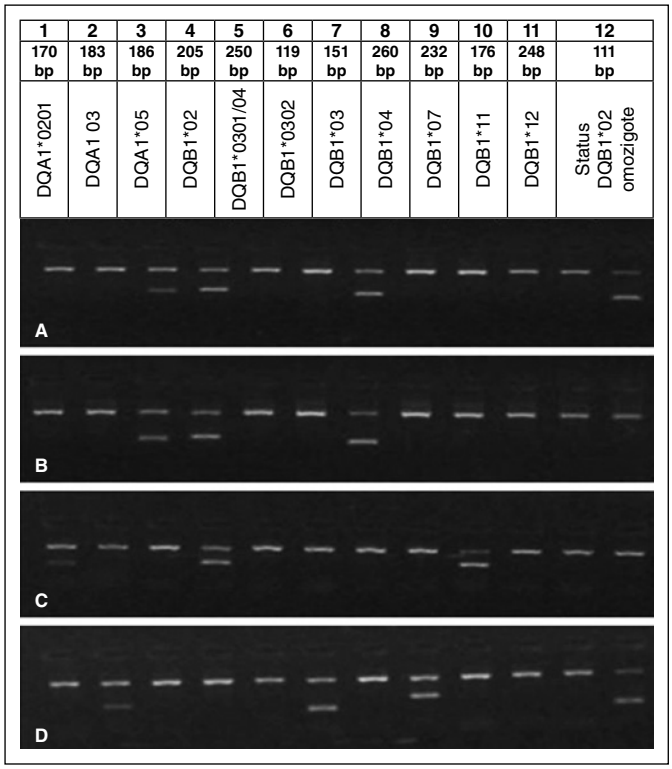

FIGURE 2. Eletrophoresis gel to classification of HLA alleles. Internal control with 796bp. (A) Presence of DQA1*05, DQB1*02, DRB1*03 alleles and the last band referred to DQB1*02 allele, meaning the absence of homozygosity - haplotype DR3-DQ2. (B) Presence of DQA1*05, DQB1*02, DRB1*03 and absence of DQB1*02- haplotype DR3-DQ2 and DQB1*02 in homozygous. (C) Presence of DQA1*0201, DQB1*02, DRB1*07 and absence of DQB1*02- haplotype DR7-DQ2 and DQB1*02 in homozygous. (D) Presence of DQA1*03, DQB1*0302, DRB1*04 and presence of DQB1*02- haplotype DR4-DQ8.

The 12th tube of the reaction identifies the DQB1*02 allele in homozygous, which is an important information, because studies reveal that homozygous haplotype, increases patient´s susceptibility to develop CD[17,21,22].

Serological assay withhuman recombinant anti-tTG

Serological dosage of human recombinant tissue transglutaminase antibody class IgA was carried out in all positive donors for HLADQ2 and DQ8 using the ELISA method. The qualitative protocol was performed according to manufacturer's instruction (IMMCO Diagnostics - Nova York - USA). The results were obtained by absorbance in double wavelength of 450/630 nm. The tests were carried out in duplicate to assure the method reproducibility, and the results extracted from the mean of the readings according to the manufacturer's guidelines. Results were considered positive when cutoff was over 25 EU/mL, negative with cutoff under 20 EU/mL, and undetermined between 20 and 25 EU/mL.

Serum determination of immunoglobulin A (IgA)

The serum IgA determination was carried out in collaboration with AFIP Medicina Laboratorial. The methodology used was nephelometry with reference values between 68.0 and 423.0 mg/dL.

Statistical analyses

The sample calculation, as well as the Fisher's exact test and thechi-square test, were carried out using CDC EPI INFO 7. The Fisher's exact test was used to assess the association between anemia and genetic predisposition. The chi-square test was used to calculate the following associations: gender and genetic predisposition; symptoms and genetic predisposition; nutritional state and genetic predisposition; genetic predisposition and human recombinant tissue transglutaminase antibody IgA class.

RESULTS

From 404 individuals included in this study, 397 were from non-anemic donors and 7 were anemic candidates for blood donation. The mean age of the candidates for blood donation was 37 years (SD=11), varying from 18 to 65 years, 209 (51.7%) were men and 195 (48.3%) were women.

Among the studied samples, 198 (49%) presented at least one of the alleles, DQ2 and/or DQ8. The distribution of DQ2 and/or DQ8 alleles among gender was similar, showing no association between gender and genetic predisposition, although CD is an autoimmune disease and thus, it is more frequent in women (Chi-square test=0.34) (P=0.559). The positive samples were associated with alleles DR3, DR4, DR7, DR11 and DR12 as showed in Table 1. The most frequent genotype was DR4-DQ8, which was present in 13.6% (55/404) of the samples, followed by the genotypes DR3-DQ2 and DR7-DQ2 with DQB1*02 in heterozygous, which are present in 10.4% (42/404) and 8.7% (34/404), respectively. There was no significant difference in the proportion of anemic donors with genetic predisposition (2.5%; 5/404) and anemic donors without genetic predisposition (1.0%; 2/404), P=0.276.

TABLE 1. DQ2 and DQ8 haplotype distribution

	n	Frequency	Total n=404
DQ2			
DQ2	5	1.2%	126 (31.2%)
DR3/DR7 - DQ2 - DQB1*02/ DQB1*02	3	0.7%	
DR7-DQ2 - DQB1*02/DQB1*02	4	1.0%	
DR3-DQ2 - DQB1*02/ DQB1*02	4	1.0%	
DR3-DQ2	42	10.4%	
DR3/DR7 - DQ2	1	0.2%	
DR3-DQ2/DR11-DQ7	8	2.0%	
DR3-DQ2/DR12 - DQ7	5	1.2%	
DR7-DQ2	35	8.7%	
DR7-DQ2/DR11 - DQ7	10	2.5%	
R7-DQ2/DR12-DQ7	9	2.2%	
DQ8			
DR4-DQ8	55	13.6%	55 (13.6%)
DQ2+DQ8			
DR3-DQ2/DR4-DQ8	7	1.7%	17 (4.2%)
DR7-DQ2/DR4-DQ8	10	2.5%	
Absence of DQ2/DQ8	206	50.9%	206 (50.9%)

Regarding the nutritional condition, no statistical difference was found, although we observed a higher frequency of underweight individuals presenting DQB1*02/ DQB1*02 (63.6%) when compared to individuals without genetic predisposition (41.3%), as shown in Table 2.

From 198 blood donors with genetic predisposition, 11 (5.5%) revealed a positive anti-tTG. This shows that 2.7% of the studied population have predisposition to CD (Table 3). No individual with serum IgA deficiency was found in the present study.

Among the 11 donors with genetic predisposition and positive anti-tTG, only 3 have some symptoms related to CD; 1 reported diarrhea and other 2 reported constipation.

TABLE 3. Amount of blood donors with genetic predisposition and antitransglutaminase tissular antibody (Anti-tTG IgA)

	Genetic predisposition			
Anti-tTGIgA	DQ2 hetero n=115	DQ2 homo n=11	DQ2+DQ8 n=17	DQ8 n=55
<25EU/mL	109 (95.6%)	10 (90.9%)	17 (100%)	51 (92.7%)
>25EU/mL	6 (5.3%)	1 (9.1%)	0 (0%)	4 (7.3%)

Fisher's exact test $P=0.476$

DISCUSSION

The present study determined HLA DQ2 and DQ8 distribution in the general population represented by the blood donors from São Paulo state. We detected that 49.1% of blood donor candidates have genetic predisposition to develop CD, since they present HLA-DQ2 and/or HLA-DQ8 alleles. Besides the genetic analysis, evaluation of antiglutaminase tissular antibody, which is considered another CD marker, was also performed. We identified 11 individuals with genetic predisposition plus anti-tTG, that represent 2.7% of the blood donors studied with high probability to develop CD. These blood donors were informed about the importance of these findings.

In addition to the blood donors, candidates for blood donation, who presented low hematocrit (Ht) at the time of screening who could not make the donation due to anemia, were enrolled in the study. It is known that anemia is a frequent condition among individuals with CD, thus, it was decided to include these individuals, in order to approximate the casuistic of this study to the general population. However, the frequency of DQ2 and DQ8 alleles among the individuals with normal Ht and low Ht was very similar.

The sensitivity (98.8%) and specificity (96.2%) verified by Clouzeau-Girard et al. through the association between genotyping for HLADQ2/DQ8 and serological markers confirms the high sensitivity of the HLA genotyping and the high specificity of the anti-tTG tests for diagnosis of children with CD. The researchers suggest that high tTG IgA rates could be sufficient to diagnose children with symptoms of CD, without the necessity of performing duodenal biopsy, and propose the HLADQ2/DQ8 genotyping to exclude the diagnosis of CD[5].

TABLE 2. Nutritional condition of blood donors with and without genetic susceptibility

	Genetic susceptibility					
BMI categories	Negative (n=206)	Positive (n=198)				
		DQ2 hetero (n=115)	DQ2 homo (n=11)	DQ2+DQ8 (n=17)	DQ8 (n=55)	Total
Underweight	87 (42.3%)	48 (41.7%)	7(63.6%)	8 (47.1%)	26 (47.2%)	89 (44.6%)
Normal weight	76 (36.9%)	48 (41.7%)	2 (18.2%)	5 (29.4%)	21 (38.1%)	76 (38.5%)
Overweight	30 (14.6%)	16 (13.9%)	2 (18.2%)	4 (23.5%)	6 (10.9%)	28 (14.2%)
Obesity	13 (21.8%)	3 (2.6%)	0	0	2 (3.6%)	5 (3.0%)

On the other hand, Megiorni et al. observed that among Italian patients with CD, 8.9% were negative for HLA DQ2 and DQ8. In these individuals, the frequency of the DQB1*02, DQA1*05 alleles and none of the two alleles were 66.7%, 23.1% and 10.2%, respectively, compared to 14.1%, 53.4% and 32.5% of controls. Thus, there was a positive association between CD and phenotype β2 (B1*02/X or B1*02/02) and a negative association to phenotype α5 (A1*0501 in the absence of DQB1*02) [23].

A Brazilian study also found CD patients with confirmed diagnostic after duodenal biopsies presenting HLA-DQ2 e HLA-DQ8 both negative[16]. Therefore in our study we may not detected any CD donor since we evaluate the anti-tTG antibody levels just in those donors positive to HLA-DQ2 and/or HLA-DQ8. However, a lot of studies showed a strong relation between this genetic markers to the development of CD and both studies aforementioned[16,23] showed the negative relation in less than 10% of the cases.

Different results were obtained in other studies. Donat et al. in Spain, who observed that the association with CD can be attributed to the complete haplotype (DR3-DQA1*0501 DQB1*0201), and no stronger association with DQB1*0201 allele was related[8]. Molecular results, here obtained, showing that 49.9% of studied blood donors have genetic predisposition for CD, represent a high frequency if compared with studies carried out in other countries, such as in Finland where the genetic predisposition was observed in 38.9%, being 21% DR4-DQ8 and 16% DR3-DQ2 (13). Another study performed in the Middle East, in Jordan, concluded hat the most frequent haplotype in that population, as well as in our study, is DR4-DQ8, but presenting a frequency of 17.9%[29].

Other studies showed lower prevalence as in Israel with 1:157[32], 1:166 in Iran[31], 1:179 in India[15] and 1:700 Tunisia[2], in which probably the data were underestimated, since these studies were performed with large male populations. As CD is an autoimmune disease and thus, more frequent in women, it would be expected that higher prevalence of the disease in women.

In addition, two other studies evaluated genetic susceptibility to CD in Brazilians, however both of them were performed in CD patients' relatives. Castro-Antunes et al. found genetic predisposition in 78.6% of the patients' relatives in the North East region[4], and a study performed in the Center West region by Martins et al., described the DQ2 allele in 42% of the relatives, being DQ2 associated to DRB1*04 in 13% and DRB1*04 alone in 4.6% of the individuals[19]. However, since the studies were performed in relatives, it was not possible to detect the real genetic predisposition for CD in the Brazilian general population.

In a 2012 Brazilian study involving 452 adult individuals from different regions of the country, using the same kit used in the present study, prevalence of DQ2 and/or DQ8 was similar to our results. HLA-DQ2 was identified in 160 (35.4%) individuals, DQ8 in 57 (12.6%) and DQ2/DQ8 in 18 (4%). Among the individuals identified with HLA-DQ2, the most frequent (65 cases, 40.6%) was DR3-DQ2 with DQB1*02 in heterozygosis, followed by DR7-DQ2 haplotype with DQB1*02 in heterozygosis identified in 47 individuals (29.4%). Among the individuals found with DQ8 haplotype, the most frequent was DR4-DQ8, 42 (73.7%), followed by 15 (26.3%) individuals with DR4-DQ8/DQ7. The most frequent DQ2 + DQ8 haplotype was DR7-DQ2/DR4-DQ8 with 13 (72.2%) individuals. DQB1*02 homozygous was found in 23 (14.4%) cases, slightly higher than our findings[30].

In a systematic review, reported in 2013, HLA-DQ2 antigen was reported in 5% to 10% of the Chinese and the Sub-Saharan Africans compared to 20% in West Europe. HLA-DQ8, which is present in less than 5% of West Europeans, Americans and Asians, was found in 5%-10% of English, Tunisians and Iranians[14].

In Brazil, as well as in other Latin America countries, the high cost of the genotyping for CD and the lack of skill labor are limitations to apply the genotyping in the CD diagnostic. Therefore, serological tests accompanied by and duodenal biopsy are still mandatory to confirm the diagnosis of CD. Some Brazilian studies[3,7,10,11,24,26,27,28,37] showed high CD prevalence through the evaluation of the level of anti-transglutaminase and duodenal biopsy, including 1:214 in São Paulo[26], 1:273 in Riberão Preto[24], 1:417 in Curitiba[27] and 1:681 in Brasilia[10].

Despite the challenges to perform molecular tests in the routine diagnostics, it is clear that it will be important to avoid the invasive method as the duodenal biopsy to conclude the CD diagnostic. The new guidelines of the European Society of Pediatric Gastroenterology (ESPGHAN) suggests that duodenal biopsy is not necessary in symptomatic patients with genetic predisposition to HLA-DQ2 and/or DQ8 and anti-transglutaminase levels higher than 10 times the reference value[13].

A limitation of the present study was the unavailability of duodenal biopsy in 11 donors that have DQ-2 and DQ-8 presence and positive anti-tTG. These donors were contacted by doctors to be evaluated clinically and possible duodenal biopsy would be performed. However, we did not have the donors return yet.

In conclusion, the prevalence of the genetic markers for CD, HLA-DQ2 and DQ8 in São Paulo showed to be as high and similar as to that found in Europe. The serum prevalence for CD in the blood donor's positive for HLA-DQ2 and DQ8 was high. These findings allow us to state that the prevalence of CD is not a rare disease, but most probably underdiagnosed in our population.

Authors' contributions

Muniz JG: study design; data collection; performing all tecniques procedures; manuscript writing; statistical analysis; responsible for the process of submitting the article; responsible for the translation into English and text formatting. Sdepanian VL: study design, statistical analysis; revision of the article writing. Fagundes Neto U: study design; revision of the article writing and translation.

Muniz JG, Sdepanian VL, Fagundes Neto U. Prevalência da predisposição genética para doença celíaca nos doadores de sangue em São Paulo, Brasil. Arq Gastroenterol. 2016,53(4):267-72.

RESUMO - ***Contexto*** - A doença celíaca é uma enteropatia imuno mediada causada pela intolerância permanente induzida pelo glúten, que se expressa por enteropatia mediada por linfócitos T, e possui uma alta prevalência na população geral. Há evidências de forte predisposição genética para doença celíaca. ***Objetivo*** - Determinar a prevalência dos marcadores genéticos HLA-DQ2 e HLA-DQ8 em doadores de sangue da cidade de São Paulo e realizar rastreamento sorológico para doença celíaca com anticorpo antitransglutaminase tissular recombinante humana de classe IgA naqueles doadores de sangue com genotipagem HLA-DQ2 e HLA-DQ8 positivos. ***Métodos*** - Estudo transversal prospectivo em que participaram 404 doadores de sangue, residentes na cidade de São Paulo e Jundiaí. A determinação dos alelos HLADQ2 e HLADQ8 foi realizada por PCR multiplex e alelo específico em todos os participantes do estudo e o anticorpo antitransglutaminase tissular recombinante humana de classe IgA e dosagem sérica de IgA foi realizada apenas nos doadores de sangue que possuíam DQ2 e/ou DQ8 positivo. ***Resultados*** - O HLADQ2 e/ou DQ8 foi positivo em 49% (198/404) dos indivíduos, destes, 11 (5%) apresentaram anticorpo antitransglutaminase tissular humana positivo. ***Conclusão*** - Podemos concluir que a prevalência dos marcadores genéticos para doença celíaca, HLA-DQ2 e DQ8 em São Paulo, mostrou-se elevada e similar à encontrada na Europa, assim como foi elevada a soroprevalênca para doença celíaca nos doadores de sangue com presença HLA-DQ2 e DQ8. Estes achados permitem afirmar que a prevalência da doença celíaca não deve ser rara em São Paulo, mas sim subdiagnosticada.

DESCRITORES - Doença celíaca, genética. Marcadores genéticos. Antígenos HLA-DQ. Prevalência. Doadores de sangue.

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